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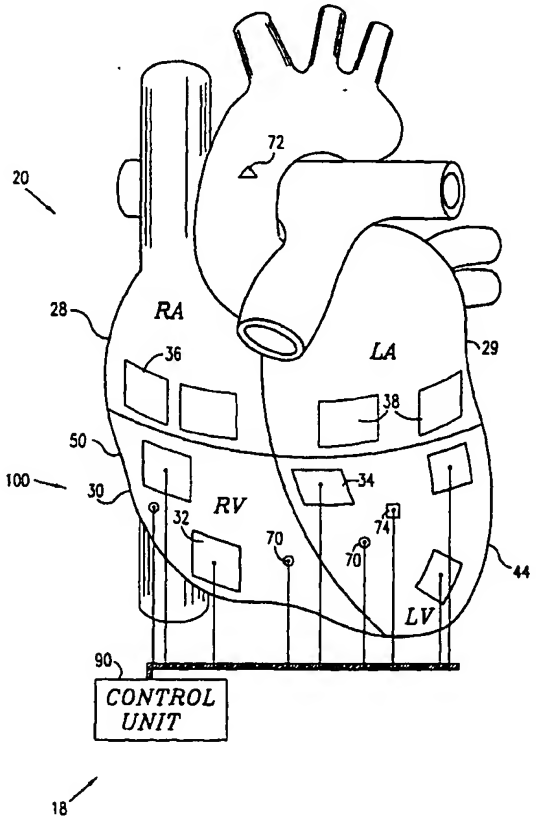

(57) Abstract: Apparatus (18) for improving the performance of the heart (20) of a human subject. A first ventricular electrode (32) is coupled to a first ventricular site of the heart, and a second ventricular electrode (34) is coupled to a second ventricular site of the heart. A control unit (90) drives the first ventricular electrode to apply one or more paired pulses at the first ventricular site and drives the second ventricular electrode to apply one or more paired pulses at the second ventricular site.

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CARDIAC CONTROL USING PAIRED PACING

FIELD OF THE INVENTION

The present invention relates generally to invasive devices and methods for treatment of the heart, and specifically to devices and methods for improving cardiac performance.

BACKGROUND OF THE INVENTION

The human body normally regulates the cardiac output in response to body needs by changing the heart rate, as during physical exercise, and/or by adapting the stroke volume. Under pathological conditions, however, some of the normal regulatory mechanisms may be damaged. For example, heart tissue damaged due to myocardial infarct typically cannot sustain normal pumping function. Alternatively or additionally, physiological electrical signals are not generated, or are impaired in their propagation, and cardiac output or cardiac efficiency (stroke work divided by oxygen consumption) is correspondingly compromised. Standard pacemakers known in the art are able to control the rate of the heart, e.g., to accelerate the heart rate after detecting bradycardia, but are not able to increase contraction strength over the long-term without producing adverse side-effects.

Application of paired or coupled pacing pulses to the heart is known to produce a phenomenon called post-extrasystolic potentiation (PESP), in which the contraction force of the heart increases. A paired pulse is an additional electric pulse applied to the heart a short time after an artificially-applied pacing pulse, for example, 300 ms thereafter. A coupled pacing pulse is similar, except that it is applied after a naturally-generated activation pulse. In the context of the present patent application, the term "paired pulse" refers generally to both paired and coupled pulses.

In an article, "Postextrasystolic potentiation: Do we really know what it means and how to use it?" by M. Cooper, in *Circulation*, **88**(6), December 1993, which is incorporated herein by reference, it is noted that induction of PESP is not used clinically because: (1) it is difficult to wean a failing ventricle from paired pacing, (2) oxygen consumption significantly increases, (3) there is an increased risk of developing ventricular arrhythmias, and (4) there is a risk of increasing the ventricular failure which is nominally being treated.

US patent 5,212,098, to Bennett et al., which is incorporated herein by reference, describes a method for applying paired pacing pulses to the right atrium and/or the right ventricle, to induce PESP. Also described is a method for inducing PESP in both atria, in order to increase ventricular filling. As noted in the above-mentioned article by Cooper, however, these methods have not achieved clinical acceptance.

US patent 5,391,199 to Ben-Haim, which is also incorporated herein by reference, describes a method and apparatus for ablating a portion of the heart to treat cardiac arrhythmias. A cardiac map is generated, and one or more catheters are advanced to sites adjacent to or within the heart. The location of each catheter's distal tip is determined, and local information about the heart is sensed at the distal tip of one or more of the catheters. The sensed information is processed to create one or more data points, which are superimposed on a perspective image of the heart to enable the targeted ablation of a portion of the heart.

US patent 5,738,096 to Ben-Haim, which is incorporated herein by reference, describes a method of constructing a cardiac map, in which a probe is brought into contact with a location on a wall of the heart. The probe's position is determined at at least two different phases of the heart cycle, and local electrical and non-electrical physiological values are determined at the location. The method is repeated for a plurality of locations in the heart, and the positions are combined to form a time-dependent map of at least a portion of the heart.

SUMMARY OF THE INVENTION

It is an object of some aspects of the present invention to provide improved methods and apparatus for enhancing cardiac performance.

It is a further object of some aspects of the present invention to provide improved methods and apparatus for increasing cardiac output.

In preferred embodiments of the present invention, an electrical cardiac stimulator for improving the performance of the heart of a human subject applies paired pulses to a plurality of ventricular sites in the heart. Preferably, the sites include one or more sites in each of the left and right ventricles. Alternatively or additionally, the stimulator applies the pulses to a plurality of sites in one of the chambers of the

heart, for example, in one of the atria or one of the ventricles. The stimulator comprises two or more electrodes, preferably placed at multiple sites in or on the heart, and a control unit.

It is believed that multi-site application of paired pulses, as provided by embodiments of the present invention, induces a form of PESP which improves cardiac performance and, additionally, minimizes negative results associated with methods of PESP induction which are known in the art. In particular, it is believed that multi-site paired pacing improves cardiac efficiency by increasing stroke work substantially without increasing oxygen consumption, typically reducing the incidence of heart failure associated with methods of pacing known in the art. The increase in stroke work is enabled, according to these embodiments, by coordinating the timing of cardiac muscle contraction, typically in patients who have abnormal interventricular and/or abnormal intraventricular action potential propagation and who therefore generally demonstrate inefficient cardiac contraction. The inventors further believe that by synchronizing the timing of the electrical activity at a plurality of sites in the heart, multi-site paired pacing decreases a likelihood of development of arrhythmia.

Typically, the average stroke volume, responsive to repeated applications of paired pulses as described herein, is greater than that engendered responsive to either standard artificial pacing pulses or natural cardiac activity. Thus, use of these embodiments is appropriate, for example, for assisting a heart that is otherwise unable to satisfy immediate physiological requirements of flow rate, stroke volume, pumping efficiency, cardiac output or blood pressure.

In some preferred embodiments of the present invention, the electrodes are placed at multiple sites on the epicardium and/or endocardium of the stimulated ventricles, and, optionally, on other areas of the heart. Alternatively or additionally, one or more of the electrodes are inserted through a catheter into a coronary blood vessel and apply energy through the vessel wall to a selected area of the heart.

Typically, each electrode conveys a particular waveform to the heart, which may differ in certain aspects from the waveforms applied to other electrodes. The particular waveform to be applied to each electrode is preferably determined by the control unit, initially under the control of a physician during a calibration period of the unit. Further preferably, the cardiac stimulator (or elements thereof) is implanted in

the patient in a manner similar to that used to implant pacemakers or defibrillators known in the art. After the initial calibration period, the unit is generally able to automatically modify the waveforms as needed to maintain a desired level of performance of the stimulator. In many applications, standard pacing, cardioversion, and/or defibrillation capabilities are additionally incorporated into the stimulator.

In a preferred embodiment, one or more mechanical sensors, e.g., force transducers, strain gauges, pressure gauges, and/or motion sensors, are positioned in a vicinity of the heart, and are coupled to send mechanical-sensor signals to the control unit indicative of aspects of the heart's functioning. Alternatively or additionally, one or more physiological sensors, e.g., for measuring blood pH, mixed venous oxygen saturation (SvO2) or thoracic electrical impedance, send physiological-sensor signals to the control unit. The various sensor signals serve as feedback to enable the control unit to iteratively adjust the paired pulses applied to one or both of the ventricles and to compare newly-measured signals with desired values. Alternatively or additionally, other sensors, such as sensing electrodes, blood pressure or flow sensors, are coupled to the heart or elsewhere on the patient's body, and send signals to the control unit which are used in determining modifications to parameters of the applied paired pulses. Further alternatively or additionally, the control unit analyzes the sensor signals to detect an onset of arrhythmia, and modifies or terminates application of the paired pacing pulses responsive to the detection.

There is therefore provided, in accordance with a preferred embodiment of the present invention, a method for improving the performance of the heart of a human subject, including:

applying one or more paired pulses at a first ventricular site of the heart; and

applying one or more paired pulses at a second ventricular site of the heart.

Preferably, the paired pulses are applied to at least the first site so as to induce post-extrasystolic potentiation.

In a preferred embodiment, applying the paired pulses at the first and second ventricular sites includes applying paired pulses at sites on one ventricle of the heart. Alternatively, applying the paired pulses at the first ventricular site includes applying one or more pulses to one of the ventricles of the heart, and applying the paired pulses

at the second ventricular site includes applying one or more pulses to the other ventricle of the heart.

Typically, the paired pulses are applied to at least the first site so as to increase cardiac output. Alternatively or additionally, the paired pulses are applied to at least the first site so as to increase blood pressure generated by the heart. Further alternatively or additionally, the paired pulses are applied to at least the first site so as to increase efficiency of the heart.

In a preferred embodiment, the method includes:

sensing activity of the heart to detect an arrhythmia thereof; and

applying antiarrhythmic electrical energy to the heart to treat the arrhythmia.

Preferably, the paired pulses applied at the first site include:

an artificially-applied pacing pulse; and

a pulse applied at a designated interval following application of the pacing pulse.

Alternatively or additionally, the method includes detecting a naturally-generated activation pulse. Preferably, applying the one or more paired pulses at the first site includes applying at the first site a coupled pulse at a designated interval following the naturally-generated activation pulse.

In a preferred embodiment, the first ventricular site is one of a plurality of test sites, and the method includes:

applying paired pulses at each of the test sites during a calibration period;

evaluating a response of the heart to the paired pulses applied during the calibration period, so as to determine one or more effective sites for subsequent application of the paired pulses; and

applying paired pulses at the one or more effective sites responsive to the evaluation.

In a preferred embodiment, the paired pulses are applied at at least one of the sites so as to reduce a potential for arrhythmia.

Alternatively or additionally, the method includes:

sensing activity of the heart to detect an arrhythmia thereof; and

terminating application of the paired pulses to at least the first site responsive to the detection.

In a preferred embodiment, detecting the arrhythmia includes detecting at least one ectopic heart beat.

In a preferred embodiment, the method includes applying one or more pacing pulses at a pacing site of the heart.

Preferably, applying the paired pulses at the first site includes:

applying one or more pacing pulses at the first site during a calibration period;

evaluating at a plurality of detection sites a response of the heart to the one or more pacing pulses applied during the calibration period, so as to determine one or more effective sites for subsequent application of paired pulses; and

during a regular operation period subsequent to the calibration period, applying at the first site one or more regular operation pacing pulses and applying at the one or more effective sites one or more pulses paired to the regular operation pacing pulses.

Further preferably, the response of the heart includes a mechanical response or an electrical response. Alternatively or additionally, evaluating the response of the heart includes measuring the response later than about 50 ms subsequent to application of the pacing pulses. Further alternatively or additionally, evaluating the response of the heart includes measuring the response later than about 200 ms subsequent to application of the pacing pulses.

Preferably, the method includes sensing a physiological parameter of the subject and modifying responsive thereto a characteristic of the paired pulses applied to at least the first site. Further preferably, the parameter includes a mechanical or an electrical characteristic of the heart. Alternatively or additionally, the parameter includes blood pressure of the subject, the concentration of a gas in the blood of the subject, or blood pH.

There is further provided, in accordance with a preferred embodiment of the present invention, apparatus for improving the performance of the heart of a human subject, including:

a first ventricular electrode, coupled to a first ventricular site of the heart;

a second ventricular electrode, coupled to a second ventricular site of the heart; and

a control unit, which drives the first ventricular electrode to apply one or more paired pulses at the first ventricular site and drives the second ventricular electrode to apply one or more paired pulses at the second ventricular site.

In a preferred embodiment, the apparatus includes a sensor, coupled to detect arrhythmia of the heart and to convey a signal responsive thereto to the control unit. Preferably, the control unit applies antiarrhythmic energy to the heart to treat the arrhythmia.

In a preferred embodiment, the control unit drives at least the first electrode to apply the pulses so as to increase efficiency of the heart.

Preferably, the paired pulses applied by at least the first electrode include:

an artificially-applied pacing pulse; and

a pulse applied at a designated interval following application of the pacing pulse.

Alternatively or additionally, the control unit detects a naturally-generated activation pulse, and drives at least the first electrode to apply at the first site a coupled pulse, at a designated interval following the naturally-generated activation pulse.

In a preferred embodiment, the first ventricular site is one of a plurality of test sites, and the first electrode is coupled in turn to each of the test sites during a calibration period. Preferably, the control unit drives the first ventricular electrode to apply paired pulses at each of the test sites during the calibration period, and evaluates a response of the heart to the paired pulses applied during the calibration period to determine one or more effective sites for subsequent application of the paired pulses.

In a preferred embodiment, the apparatus includes a pacing electrode, coupled to a pacing site of the heart, and the control unit drives the pacing electrode to apply pacing pulses to the pacing site.

Preferably, the control unit drives at least one of the ventricular electrodes to apply the paired pulses so as to reduce a potential for arrhythmia.

Alternatively or additionally, the apparatus includes a sensor, coupled to detect arrhythmia of the heart and to convey a signal responsive thereto to the control unit. Preferably, the control unit terminates application of the paired pulses to at least one of

the ventricular sites responsive to the signal. In a preferred embodiment, the arrhythmia includes at least one ectopic heart beat.

Preferably, the control unit drives the first ventricular electrode to apply one or more pacing pulses at the first site during a calibration period, and evaluates at a plurality of detection sites a response of the heart to the one or more pacing pulses applied during the calibration period, so as to determine one or more effective sites for subsequent application of paired pulses. Further preferably, the apparatus includes one or more paired-pulse electrodes, which are respectively coupled to the one or more effective sites responsive to the determination. Still further preferably, during a regular operation period subsequent to the calibration period, the control unit drives the first ventricular electrode to apply at the first site one or more regular operation pacing pulses, and drives the one or more paired-pulse electrodes at the one or more effective sites to apply one or more pulses paired to the regular operation pacing pulses. Typically, the response of the heart includes a mechanical or an electrical response. In a preferred embodiment, during the calibration period, the control unit measures the response later than about 50 ms subsequent to application of the pacing pulses.

Preferably, the apparatus includes at least one sensor coupled to the subject's body, which senses a physiological parameter of the subject and conveys to the control unit a sensor signal responsive thereto. Further preferably, the control unit modifies responsive to the sensor signal a characteristic of the paired pulses applied to at least one of the ventricular sites. In a preferred embodiment, the sensor is selected from the list consisting of: a motion sensor, an accelerometer, a strain gauge, a force transducer, an ECG sensor, a left ventricular pressure sensor, a blood pressure sensor, a thoracic electrical impedance sensor, an SvO2 sensor, a pH sensor, a pO2 sensor, a pCO2 sensor, an electrical activity sensor, and a blood flow rate sensor.

There is still further provided, in accordance with a preferred embodiment of the present invention, a method for improving the performance of the heart of a human subject, including:

applying one or more paired pulses at a first site of a chamber of the heart; and

applying one or more paired pulses at a second site of the chamber.

In a preferred embodiment, the first site is one of a plurality of test sites, and the method includes:

applying paired pulses at each of the test sites during a calibration period;

evaluating a response of the heart to the paired pulses applied during the calibration period to determine one or more effective sites for subsequent application of the paired pulses; and

applying paired pulses at the one or more effective sites responsive to the evaluation.

Alternatively or additionally, applying the paired pulses at the first site includes:

applying one or more pacing pulses at the first site during a calibration period;

evaluating at a plurality of detection sites a response of the heart to the one or more pacing pulses applied during the calibration period, so as to determine one or more effective sites for subsequent application of paired pulses; and

during a regular operation period subsequent to the calibration period, applying at the first site one or more regular operation pacing pulses and applying at the one or more effective sites one or more pulses paired to the regular operation pacing pulses.

There is yet further provided, in accordance with a preferred embodiment of the present invention, apparatus for improving the performance of the heart of a human subject, including:

a first electrode, coupled to a first site of a chamber of the heart;

a second electrode, coupled to a second site of the chamber; and

a control unit, which drives the first electrode to apply one or more paired pulses at the first site and drives the second electrode to apply one or more paired pulses at the second site.

There is also provided, in accordance with a preferred embodiment of the present invention, apparatus for improving the performance of the heart of a human subject using a first ventricular electrode and a second ventricular electrode, coupled respectively to a first ventricular site and a second ventricular site of the heart, the apparatus including a control unit, which drives the first ventricular electrode to apply one or more paired pulses at the first ventricular site and drives the second ventricular electrode to apply one or more paired pulses at the second ventricular site.

There is additionally provided, in accordance with a preferred embodiment of the present invention, apparatus for improving the performance of the heart of a human

subject using a first electrode, coupled to a first site of a chamber of the heart, and a second electrode, coupled to a second site of the chamber, the apparatus including a control unit, which drives the first electrode to apply one or more paired pulses at the first site and drives the second electrode to apply one or more paired pulses at the second site.

The present invention will be more fully understood from the following detailed description of the preferred embodiments thereof, taken together with the drawings, in which:

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic illustration of the external surface of a heart, showing the placement of electrodes and sensors thereon, in accordance with a preferred embodiment of the present invention; and

Fig. 2 is a schematic block diagram of a control unit, which generates signals to be applied to the electrodes shown in Fig. 1, in accordance with a preferred embodiment of the present invention.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Fig. 1 is a schematic illustration of cardiac control apparatus 18, which applies electrical energy to improve the performance of the heart 20 of a patient, in accordance with a preferred embodiment of the present invention. Apparatus 18 preferably comprises an implantable or external control unit 90, which applies paired pulses through multiple electrodes 100, comprising one or more electrodes 32, electrically coupled to the right ventricle 30, and/or to one or more electrodes 34, electrically coupled to the left ventricle 44 of heart 20. Alternatively or additionally, paired pulses are applied to the right and/or left atria 28 and 29 through respective electrodes 36 and 38 coupled to the control unit. (As defined in the Background section, the term "paired pulse" refers herein generally to both paired and coupled pulses.)

Typically, the average stroke volume of cardiac muscle tissue exposed to repeated applications of the paired pulses is greater than that generated responsive to either standard artificial pacing pulses or natural cardiac activity. Thus, use of this

embodiment is appropriate, for example, for assisting a heart that is otherwise unable to satisfy immediate physiological requirements of cardiac output or blood pressure.

Electrodes 100 are typically coupled to epicardium 50 overlying the ventricles. Electrodes 100 may also be coupled to the endocardium or to other suitable locations in or on the patient's body. In some applications, it is desirable to insert one or more of electrodes 100 into a blood vessel in a vicinity of ventricle 30 or 44.

Control unit 90 is also optionally coupled to one or more local sense electrodes 74, which are placed on or in the heart and convey electrical signals responsive to cardiac electric activity. Alternatively or additionally, one or more of electrodes 100 and any of the other electrodes coupled to control unit 90 may also serve as sense electrodes. Optionally, one or more mechanical sensors 70 (e.g., accelerometers, force transducers, strain gauges, or pressure gauges), coupled to the control unit, are placed on the ventricles or elsewhere on the heart. Further optionally, one or more supplemental sensors 72 (e.g., blood pressure, thoracic electrical impedance, SvO2, pH, pCO2 or pO2 sensors) are coupled to the control unit and are placed on or in the heart or elsewhere on or in the patient's body. Preferably, the control unit modifies the energy applied through electrodes 100, 36 and/or 38 responsive to signals from sensors 70 and 72 and local sense electrodes 74, as described hereinbelow. Typically, control unit 90 and the above-mentioned electrodes and sensors are permanently or semi-permanently implanted in or coupled to the patient's body. (For clarity, connections between control unit 90 and only some of the electrodes and sensors are shown in Fig. 1.)

The placement and number of electrodes and sensors are shown in Fig. 1 by way of example. Other sites on heart 20 or in a vicinity thereof are appropriate for electrode and sensor placement in other applications of the present invention. Different types of electrodes known in the art are typically selected based on the specific condition of the patient's heart, and may comprise coil, defibrillation, screw, patch, basket, needle and/or wire electrodes, or substantially any other electrode known in the art of electrical stimulation or sensing in tissue. In a preferred embodiment, an electrode is passed through the coronary sinus and positioned so as to stimulate the left ventricle or another chamber of the heart. Alternatively or additionally, one or more of the electrodes are placed during an endoscopic procedure or during open chest surgery.

Preferably, control unit 90 is implanted in the patient in a manner similar to that used to implant pacemakers or defibrillators known in the art, such that after an initial calibration period, described hereinbelow, the unit is generally able to automatically modify the pulses it applies to the heart as needed to maintain a desired level of performance. In many applications, pacing, cardioversion, and defibrillation capabilities are additionally incorporated into apparatus 18.

Fig. 2 is a schematic block diagram of control unit 90, in accordance with a preferred embodiment of the present invention. Mechanical sensors 70, supplemental sensors 72, local sense electrodes 74, and electrodes 100 are preferably coupled to provide feedback signals to a cardiac function analysis block 80 of control unit 90. The feedback signals generally provide information about various aspects of the heart's performance to block 80, which analyzes the signals and actuates control unit 90 to modify the electrical energy applied to the heart responsive to the analysis. Preferably, the paired pulses are adjusted by the control unit responsive to the feedback signals in order to yield a desired response, e.g., a predetermined blood pressure, blood oxygen level, cardiac output and/or cardiac electrical or motion profile. It will be understood that the arrangement of inputs to the control unit as shown in Fig. 2 is by way of illustration and not limitation. In another preferred configuration, electrodes 36 and/or 38 are coupled to the control unit, in parallel with or instead of electrodes 100.

Preferably, block 80 conveys results of its analysis to a "parameter search and tuning" block 84 of control unit 90, which iteratively modifies characteristics of the electrical signals applied to the heart in order to attain a desired response. Preferably, operating parameters of block 84 are entered by a human operator of the control unit using operator controls 71, which typically comprise a keyboard or mouse (not shown) coupled to the control unit. Block 84 typically utilizes multivariate optimization and control methods known in the art in order to cause one or more of the aforementioned mechanical, electrical, chemical and/or other measured parameters to converge to desired values.

In general, each one of electrodes 100 may convey a particular waveform to heart 20, differing in certain aspects from the waveforms applied by the other electrodes. The particular waveform to be applied by each electrode is determined by control unit 90, preferably under the control of the operator. Aspects of the waveforms which are set by the control unit, and may differ from electrode to electrode, typically

include parameters such as time shifts between application of waveforms at different electrodes, waveform shapes, amplitudes, DC offsets, durations, and duty cycles. For example, although the waveforms applied to some or all of electrodes 100 usually comprise a monophasic square wave pulse following a natural or applied pacing pulse, other waveforms, such as a sinusoid, a series of biphasic square waves, or a waveform including an exponentially-varying characteristic, could be applied to other electrodes. Generally, the shape, magnitude, and timing of the waveforms are optimized for each patient, using suitable optimization algorithms as are known in the art.

For the purposes of this embodiment of the present invention, block 84 typically modifies a set of controllable parameters of the paired pulses, responsive to the measured parameters, in accordance with values in a look-up table and/or pre-programmed formulae stored in an electronic memory of control unit 90. The controllable parameters may comprise, for example, pulse timing, magnitude, offset, and monophasic or biphasic shape. Preferably, the controllable parameters are conveyed by block 84 to a signal generation block 86 of control unit 90, which generates, responsive to the parameters, electrical signals that are applied by electrodes 100 to ventricles 30 and 44. Block 86 preferably comprises amplifiers, isolation units, and other standard circuitry known in the art of electrical signal generation.

In the initial calibration procedure, parameter search and tuning block 84 preferably modifies a characteristic (e.g., timing, magnitude, and/or shape) of the paired pulses applied through one of electrodes 100, 36 and/or 38, and then determines whether a predetermined cardiac functional response generally improves following the modification. In a series of similar calibration steps, block 84 repeatedly modifies characteristics of the signals applied through each of the electrodes, such that those modifications that improve the response are generally maintained, and modifications that cause it to worsen are typically eliminated or avoided.

Preferably, the calibration procedure is subsequently performed by a physician at intermittent follow-up visits, and/or by unit 90 automatically during regular use of the apparatus (e.g., daily). When apparatus 18 is calibrated in the presence of a physician, it is often desirable to have the patient perform increasing levels of exercise (e.g., walk on a treadmill), in order to derive a broader range of operating parameters, which are stored in control unit 90 and can be accessed responsive to signals from the sensors and electrodes coupled to the control unit.

In a preferred embodiment, the calibration procedure comprises the application of standard (non-paired) pacing pulses at some sites, in conjunction with the application of paired pulses at other sites, so as to determine, by means of standard optimization methods known in the art, (a) a first set of sites, in one or more of the chambers of heart 20, in which standard pacing pulses improve the cardiac functional response, and (b) an additional set of sites, in one or more of the chambers, in which paired pacing pulses improve the response, particularly when applied in conjunction with the standard pacing pulses. Preferably, the procedure additionally comprises determining a schedule for the application of paired and standard pacing pulses at the various sites during regular operation. For example, a left ventricular site may exclusively be stimulated by paired pacing pulses, a right ventricular site only by standard pacing pulses, and a right atrial site may alternate between paired and standard pulses, according to the schedule generated during the calibration procedure.

Alternatively or additionally, during the initial calibration procedure, the locations of one or more of electrodes 100, 36, and/or 38 are varied while signals are applied therethrough, so as to determine optimum placement of the electrodes. By way of example and not limitation, the physician may initially place one of electrodes 32 on epicardium 50 of right ventricle 30, and determine the electrical and/or mechanical response of heart 20. Preferably, methods for measuring the heart's response include electrocardiography, echocardiography, and/or methods having as inputs the outputs of mechanical and supplemental sensors 70 and 72. In subsequent steps, the electrode is moved over an area of the right ventricle, and the response of the heart is measured. After the physician considers that a sufficient number of sites have been investigated to characterize the area of the ventricle, the electrode is returned to the site yielding the best response. Subsequently, other electrodes placed on, in, or near the right ventricle or other chambers of the heart are moved according to the same protocol, so as to achieve substantially optimum placement of some or all of the electrodes.

Further alternatively or additionally, pacing pulses are applied at a first site during the calibration period, and an electrical and/or mechanical cardiac functional response to the pacing pulse is measured at a plurality of detection sites. Typically the measurements enable a determination of which of the detection sites generate the response excessively late with respect to the pacing pulse, e.g., later than approximately 200 ms following the pacing pulse, or, alternatively, later than only 50

ms following the pacing pulse. In a preferred embodiment, electrodes are placed at one or more of the detection sites showing such late activity, such that during regular operation, paired pulses may be applied at each of these detection sites. It will be appreciated that the calibration and other procedures described herein are typically applicable to any one or more of the heart's chambers.

Still further alternatively or additionally, the initial calibration procedure comprises an evaluation of data taken prior to the placement of electrodes 100, 36, and/or 38 in a vicinity of heart 20. Preferably, the initial calibration procedure includes an evaluation of ECG data to determine the nature and locations of a pathology to be treated or compensated for, by application of an embodiment of the invention.

Alternatively or additionally, data generated using techniques described in the above-referenced US patents 5,391,199 ('199) and 5,738,096 ('096) are utilized in selecting appropriate electrode sites and/or pulse application protocols. These techniques may be used to detect action potential propagation abnormalities (e.g., reduced action potential propagation speed) in one or more of the heart's chambers. The cardiac dysfunction is typically observed via an electrical and/or mechanical activation map which is generated using techniques described in the '199 and/or '096 patents. Preferably, the electrical activation map shows at least one site whose electrical activation is later than, for example, 50 ms or 70 ms subsequent to a first detected ventricular activation, and an electrode is placed at that site and/or at one or more sites on the map demonstrating the greatest delays in activation.

In combination with the use of the electrical activation map, or independent thereof, the mechanical activation map may be analyzed to determine suitable sites for electrode placement. In a preferred embodiment, a mechanical characteristic such as muscle thickness or local contraction strength is assessed in combination with the electrical activation map when deciding electrode placement locations. Thus, two sites, which each show a delay of 70 ms, may differ mechanically such that only one of the sites is selected to have an electrode coupled thereto. Preferably, electrodes are coupled to the heart to apply paired pulses, as described hereinabove, in such a manner as to minimize or eliminate an observed dysfunction and restore normal contraction. Typically, an analysis of ECG data and/or of data obtained via applying the techniques of the '199 or the '096 patents is used to define an initial electrode placement and

paired-pulse application strategy, and this is subsequently refined using some of the other calibration techniques described hereinabove.

Most preferably, during calibration and during regular operation of control unit 90, an arrhythmia detection block 82 of control unit 90 receives inputs from sensors 70 and 72 and electrodes 74 and 100, and/or other electrodes and sensors (not shown), and evaluates these inputs to detect an onset of cardiac arrhythmia, e.g., an ectopic heartbeat, fibrillation, bradycardia or heart block. Preferably, block 82 employs techniques known in the art for detecting arrhythmias, so that parameter search and tuning block 84 can treat or terminate the arrhythmia by applying, for example, regular pacing pulses or defibrillation pulses, and/or by discontinuing application of the paired pulses. In a preferred embodiment, two sets of parameters are stored in control unit 90, respectively representing ectopic and non-ectopic heart behavior. Detection block 82 preferably analyzes the outputs of the various electrodes and sensors with respect to the two parameter sets, and applies paired pulses only after determining that substantially no ectopic behavior is present.

In a preferred embodiment, application of the paired pulses is accompanied by artificial pacing pulses, which are preferably applied to electrodes 100 before application of the paired pulses thereto. For example, one of the ventricles may be stimulated with a standard pacing pulse and subsequently with a paired pulse. The other ventricle may also be stimulated with artificial pacing pulses and paired pulses, or, alternatively, with pulses coupled to naturally-generated pacing pulses.

In other preferred embodiments, however, the sinoatrial node generates the cardiac rhythm, substantially without artificial pacing. In such modes, local sense electrodes 74 and, optionally, some or all of electrodes 100, convey electrical signals to control unit 90, so as to enable parameter search and tuning block 84 to synchronize the electrical signals applied by electrodes 100 with the natural electrical activity of the heart. Responsive to the detected electrical activity, artificial pulses coupled in time to the natural pulses are applied to one or both ventricles. It will be understood that although electrodes 74 and 100 are shown for clarity of explanation as separate entities, a single set of electrodes may be used to perform both functions.

In some operational modes, one of the ventricles is stimulated at multiple sites, while the other ventricle is substantially not artificially stimulated at all. In other modes, each ventricle is stimulated at one or more locations thereof.

Preferably, the paired pulses have generally the same magnitude and shape as pacing signals known in the art. Further preferably, the time interval between a first pulse (natural or artificial) and a second pulse which is paired to the first pulse is approximately 80-400 ms, typically between about 100 and 200 ms. Typically, when the heart is artificially paced, the first pulse is applied at all designated ventricular sites substantially simultaneously. In a preferred embodiment, both ventricles are paced, and an interventricular delay typically not exceeding 50-100 ms is set between a pacing pulse applied in one of the ventricles and a pacing pulse applied in the other ventricle. Preferably, the delay is determined during the initial calibration procedure. In other embodiments, the timing of application of the pulses at the various sites is individually determined for each site.

It will be appreciated by persons skilled in the art that the present invention is not limited to what has been particularly shown and described hereinabove. Rather, the scope of the present invention includes both combinations and sub-combinations of the various features described hereinabove, as well as variations and modifications thereof that are not in the prior art which would occur to persons skilled in the art upon reading the foregoing description.

CLAIMS

1. A method for improving the performance of the heart of a human subject, comprising:

applying one or more paired pulses at a first ventricular site of the heart; and

applying one or more paired pulses at a second ventricular site of the heart.

2. A method according to claim 1, wherein applying the one or more paired pulses at the first ventricular site comprises applying the one or more paired pulses at the first ventricular site so as to induce post-extrasystolic potentiation.

3. A method according to claim 1, wherein applying the paired pulses at the first and second ventricular sites comprises applying paired pulses at sites on one ventricle of the heart.

4. A method according to claim 1, wherein applying the paired pulses at the first ventricular site comprises applying one or more pulses to one of the ventricles of the heart, and wherein applying the paired pulses at the second ventricular site comprises applying one or more pulses to the other ventricle of the heart.

5. A method according to claim 1, wherein applying the one or more paired pulses at the first ventricular site comprises applying the one or more paired pulses at the first ventricular site so as to increase cardiac output.

6. A method according to claim 1, wherein applying the one or more paired pulses at the first ventricular site comprises applying the one or more paired pulses at the first ventricular site so as to increase blood pressure generated by the heart.

7. A method according to claim 1, wherein applying the one or more paired pulses at the first ventricular site comprises applying the one or more paired pulses at the first ventricular site so as to increase efficiency of the heart.

8. A method according to claim 1, and comprising:

sensing activity of the heart to detect an arrhythmia thereof; and

applying antiarrhythmic electrical energy to the heart to treat the arrhythmia.

9. A method according to claim 1, wherein applying the one or more paired pulses at the first ventricular site comprises:

applying an artificial pacing pulse; and

applying a pulse at a designated interval following application of the pacing pulse.

10. A method according to claim 1, and comprising detecting a naturally-generated activation pulse, wherein applying the one or more paired pulses at the first site comprises applying at the first site a coupled pulse at a designated interval following the naturally-generated activation pulse.

11. A method according to claim 1, wherein the first ventricular site is one of a plurality of test sites, and comprising:

applying paired pulses at each of the test sites during a calibration period;

evaluating a response of the heart to the paired pulses applied during the calibration period, so as to determine one or more effective sites for subsequent application of the paired pulses; and

applying paired pulses at the one or more effective sites responsive to the evaluation.

12. A method according to claim 1, wherein applying the one or more paired pulses at the first ventricular site comprises applying the one or more paired pulses at the first ventricular site so as to reduce a potential for arrhythmia.

13. A method according to claim 1, and comprising applying one or more pacing pulses at a pacing site of the heart.

14. A method according to any one of claims 1-13, and comprising:

sensing activity of the heart to detect an arrhythmia thereof; and

terminating application of the paired pulses to at least the first site responsive to the detection.

15. A method according to claim 14, wherein detecting the arrhythmia comprises detecting at least one ectopic heart beat.

16. A method according to any one of claims 1-13, wherein applying the paired pulses at the first site comprises:

applying one or more pacing pulses at the first site during a calibration period;

evaluating at a plurality of detection sites a response of the heart to the one or more pacing pulses applied during the calibration period, so as to determine one or more effective sites for subsequent application of paired pulses; and

during a regular operation period subsequent to the calibration period, applying at the first site one or more regular operation pacing pulses and applying at the one or more effective sites one or more pulses paired to the regular operation pacing pulses.

17. A method according to claim 16, wherein evaluating the response of the heart comprises evaluating a mechanical response.

18. A method according to claim 16, wherein evaluating the response of the heart comprises evaluating an electrical response.

19. A method according to claim 16, wherein evaluating the response of the heart comprises measuring, later than about 50 ms subsequent to application of one of the pacing pulses, the response generated responsive to the pacing pulse.

20. A method according to claim 19, wherein evaluating the response of the heart comprises measuring the response later than about 200 ms subsequent to application of the pacing pulse.

21. A method according to claim 19, wherein evaluating the response of the heart comprises evaluating a mechanical response.

22. A method according to claim 21, wherein evaluating the response of the heart comprises evaluating an electrical response.

23. A method according to any one of claims 1-13, and comprising sensing a physiological parameter of the subject and modifying responsive thereto a characteristic of the paired pulses applied to at least the first site.

24. A method according to claim 23, wherein sensing the parameter comprises sensing a mechanical characteristic of the heart.

25. A method according to claim 23, wherein sensing the parameter comprises sensing an electrical characteristic of the heart.

26. A method according to claim 23, wherein sensing the parameter comprises sensing blood pressure of the subject.

27. A method according to claim 23, wherein sensing the parameter comprises sensing a parameter selected from the list consisting of: the concentration of a gas in the blood of the subject and blood pH.

28. Apparatus for improving the performance of the heart of a human subject, comprising:

a first ventricular electrode, adapted to be coupled to a first ventricular site of the heart;

a second ventricular electrode, adapted to be coupled to a second ventricular site of the heart; and

a control unit, adapted to drive the first ventricular electrode to apply one or more paired pulses at the first ventricular site and to drive the second ventricular electrode to apply one or more paired pulses at the second ventricular site.

29. Apparatus according to claim 28, and comprising a sensor, adapted to be coupled to detect arrhythmia of the heart and to convey a signal responsive thereto to the control unit, wherein the control unit is adapted to apply antiarrhythmic energy to the heart to treat the arrhythmia.

30. Apparatus according to claim 28, wherein the control unit is adapted to drive at least the first electrode to apply the pulses so as to increase efficiency of the heart.

31. Apparatus according to claim 28, wherein the control unit is adapted to configure the paired pulses applied by at least the first electrode to include:

an artificial pacing pulse; and

a pulse applied at a designated interval following application of the pacing pulse.

32. Apparatus according to claim 28, wherein the control unit is adapted to detect a naturally-generated activation pulse, and to drive at least the first electrode to apply at the first site a coupled pulse, at a designated interval following the naturally-generated activation pulse.

33. Apparatus according to claim 28, wherein the first ventricular site is one of a plurality of test sites, wherein the first electrode is adapted to be coupled in turn to each of the test sites during a calibration period, and wherein the control unit is adapted to drive the first ventricular electrode to apply paired pulses at each of the test sites during the calibration period, and to evaluate a response of the heart to the paired pulses applied during the calibration period to determine one or more effective sites for subsequent application of the paired pulses.

34. Apparatus according to claim 28, wherein the control unit is adapted to drive at least one of the ventricular electrodes to apply the paired pulses so as to reduce a potential for arrhythmia.

35. Apparatus according to claim 28, and comprising a pacing electrode, adapted to be coupled to a pacing site of the heart, wherein the control unit is adapted to drive the pacing electrode to apply pacing pulses to the pacing site.

36. Apparatus according to any one of claims 28-35, and comprising a sensor, adapted to be coupled to detect arrhythmia of the heart and to convey a signal responsive thereto to the control unit, wherein the control unit is adapted to terminate application of the paired pulses to at least one of the ventricular sites responsive to the signal.

37. Apparatus according to claim 36, wherein the sensor is adapted to detect at least one ectopic heart beat.

38. Apparatus according to any one of claims 28-35, wherein the control unit is adapted to drive the first ventricular electrode to apply one or more pacing pulses at the first site during a calibration period and to evaluate at a plurality of detection sites a response of the heart to the one or more pacing pulses applied during the calibration period, so as to determine one or more effective sites for subsequent application of paired pulses,

wherein the apparatus comprises one or more paired-pulse electrodes, which are adapted to be respectively coupled to the one or more effective sites responsive to the determination, and

wherein during a regular operation period subsequent to the calibration period, the control unit is adapted to drive the first ventricular electrode to apply at the first site one or more regular operation pacing pulses and to drive the one or more paired-pulse electrodes at the one or more effective sites to apply one or more pulses paired to the regular operation pacing pulses.

39. Apparatus according to claim 38, wherein the control unit is adapted to evaluate at the plurality of detection sites a mechanical response of the heart.

40. Apparatus according to claim 38, wherein the control unit is adapted to evaluate at the plurality of detection sites an electrical response of the heart.

41. Apparatus according to claim 38, wherein during the calibration period, the control unit is adapted to measure, later than about 50 ms subsequent to application of one of the pacing pulses, the response of the heart to the pacing pulse.

42. Apparatus according to claim 41, wherein during the calibration period the control unit is adapted to measure a mechanical response of the heart.

43. Apparatus according to claim 42, wherein during the calibration period the control unit is adapted to measure an electrical response of the heart.

44. Apparatus according to any one of claims 28-35, and comprising at least one sensor adapted to be coupled to the subject's body, which is adapted to sense a physiological parameter of the subject and to convey to the control unit a sensor signal responsive thereto, wherein the control unit is adapted to modify responsive to the sensor signal a characteristic of the paired pulses applied to at least one of the ventricular sites.

45. Apparatus according to claim 44, wherein the sensor comprises a sensor selected from the list consisting of: a motion sensor, an accelerometer, a strain gauge, a force transducer, an ECG sensor, a left ventricular pressure sensor, a blood pressure sensor, a thoracic electrical impedance sensor, an SvO2 sensor, a pH sensor, a pO2 sensor, a pCO2 sensor, an electrical activity sensor, and a blood flow rate sensor.

46. A method for improving the performance of the heart of a human subject, comprising:

applying one or more paired pulses at a first site of a chamber of the heart; and

applying one or more paired pulses at a second site of the chamber.

47. A method according to claim 46, wherein applying the paired pulses at the first site comprises applying the paired pulses at the first site so as to induce post-extrasystolic potentiation.

48. A method according to claim 46, wherein applying the paired pulses at the first site comprises:

applying an artificial pacing pulse; and

applying a pulse at a designated interval following application of the pacing pulse.

49. A method according to claim 46, and comprising detecting a naturally-generated activation pulse, wherein applying the one or more paired pulses at the first site comprises applying at the first site a coupled pulse at a designated interval following the naturally-generated activation pulse.

50. A method according to claim 46, wherein the first site is one of a plurality of test sites, and comprising:

applying paired pulses at each of the test sites during a calibration period;

evaluating a response of the heart to the paired pulses applied during the calibration period to determine one or more effective sites for subsequent application of the paired pulses; and

applying paired pulses at the one or more effective sites responsive to the evaluation.

51. A method according to claim 46, wherein applying the paired pulses at one of the sites comprises applying the paired pulses so as to reduce a potential for arrhythmia.

52. A method according to claim 46, and comprising applying one or more pacing pulses at a pacing site of the heart.

53. A method according to any one of claims 46-52, and comprising:

sensing activity of the heart to detect an arrhythmia thereof; and

terminating application of the paired pulses to at least the first site responsive to the detection.

54. A method according to claim 53, wherein detecting the arrhythmia comprises detecting at least one ectopic heart beat.

55. A method according to any one of claims 46-52, wherein applying the paired pulses at the first site comprises:

applying one or more pacing pulses at the first site during a calibration period;

evaluating at a plurality of detection sites a response of the heart to the one or more pacing pulses applied during the calibration period, so as to determine one or more effective sites for subsequent application of paired pulses; and

during a regular operation period subsequent to the calibration period, applying at the first site one or more regular operation pacing pulses and applying at the one or more effective sites one or more pulses paired to the regular operation pacing pulses.

56. A method according to claim 55, wherein evaluating the response of the heart comprises evaluating a mechanical response.

57. A method according to claim 55, wherein evaluating the response of the heart comprises evaluating an electrical response.

58. Apparatus for improving the performance of the heart of a human subject, comprising:

a first electrode, adapted to be coupled to a first site of a chamber of the heart;

a second electrode, adapted to be coupled to a second site of the chamber; and

a control unit, adapted to drive the first electrode to apply one or more paired pulses at the first site and to drive the second electrode to apply one or more paired pulses at the second site.

59. Apparatus according to claim 58, wherein the control unit is adapted to configure the paired pulses applied at the first site to include:

an artificial pacing pulse; and

a pulse applied at a designated interval following application of the pacing pulse.

60. Apparatus according to claim 58, wherein the control unit is adapted to detect a naturally-generated activation pulse, and to drive at least the first electrode to apply at the first site a coupled pulse at a designated interval following the naturally-generated activation pulse.

61. Apparatus according to claim 58, wherein the control unit is adapted to drive at least one of the electrodes to apply the paired pulses so as to reduce a potential for arrhythmia.

62. Apparatus according to claim 58, and comprising a pacing electrode, adapted to be coupled to a pacing site of the heart, wherein the control unit is adapted to drive the pacing electrode to apply pacing pulses to the pacing site.

63. Apparatus according to any one of claims 58-62, and comprising a sensor, adapted to be coupled to detect arrhythmia of the heart and to convey a signal responsive thereto to the control unit, wherein the control unit is adapted to terminate application of the paired pulses to at least one of the sites responsive to the signal.

64. Apparatus according to claim 63, wherein the sensor is adapted to sense at least one ectopic heart beat.

65. Apparatus according to any one of claims 58-62, wherein the control unit is adapted to drive the first electrode to apply one or more pacing pulses at the first site during a calibration period and to evaluate at a plurality of detection sites a response of the heart to the one or more pacing pulses applied during the calibration period, so as to determine one or more effective sites for subsequent application of paired pulses,

wherein the apparatus comprises one or more paired-pulse electrodes, which are adapted to be respectively coupled to the one or more effective sites responsive to the determination, and

wherein during a regular operation period subsequent to the calibration period, the control unit is adapted to drive the first electrode to apply at the first site one or more regular operation pacing pulses and to drive the one or more paired-pulse electrodes at the one or more effective sites to apply one or more pulses paired to the regular operation pacing pulses.

66. Apparatus according to claim 65, wherein the control unit is adapted to evaluate at the plurality of detection sites a mechanical response of the heart.

67. Apparatus according to claim 65, wherein the control unit is adapted to evaluate at the plurality of detection sites an electrical response of the heart.

68. Apparatus according to claim 65, wherein during the calibration period, the control unit is adapted to measure, later than about 50 ms subsequent to application of one of the pacing pulses, the response of the heart to the pacing pulse.

69. Apparatus according to claim 68, wherein during the calibration period, the control unit is adapted to measure, later than about 50 ms subsequent to application of one of the pacing pulses, a mechanical response of the heart to the pacing pulse.

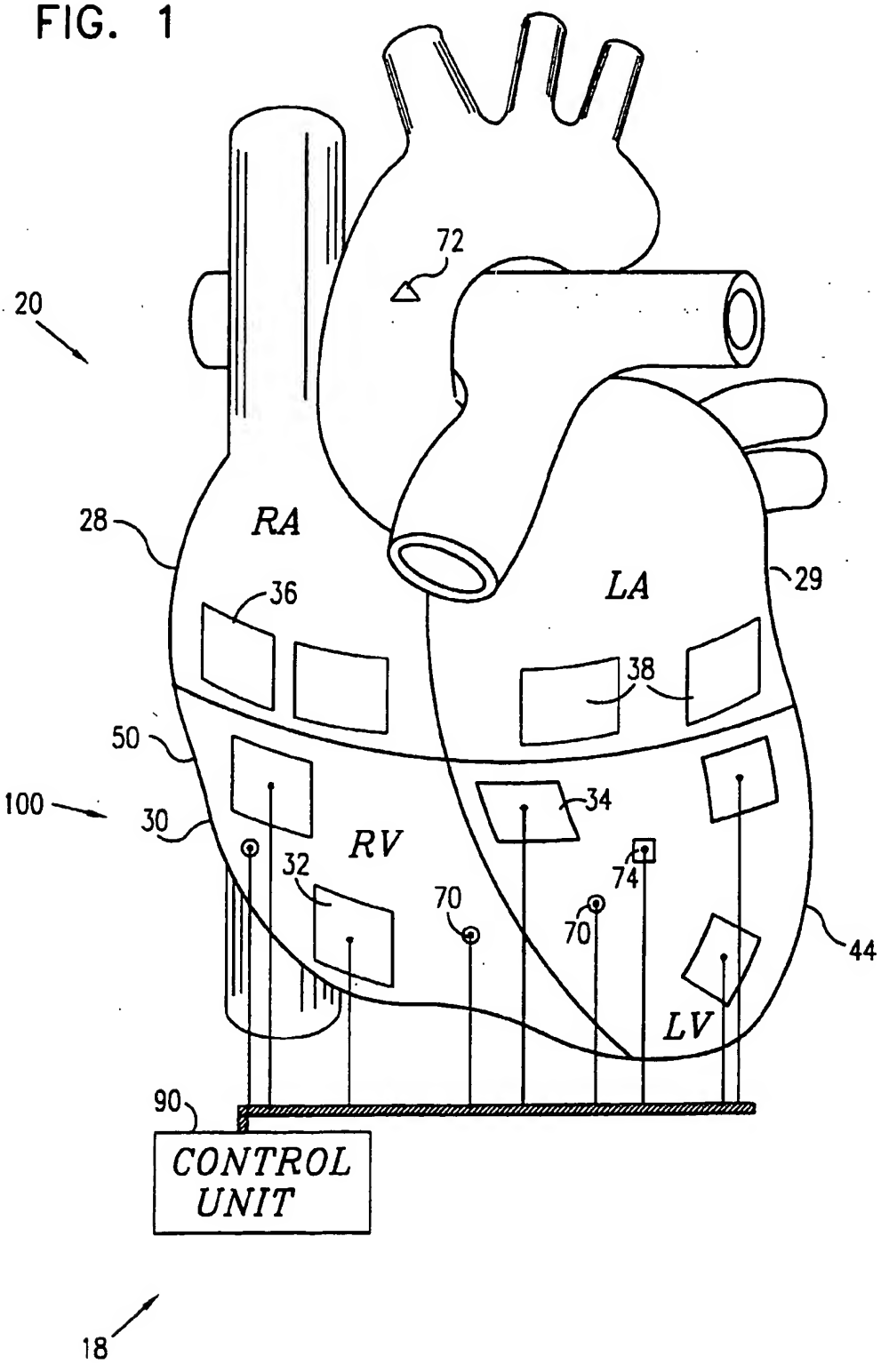
70. Apparatus according to claim 69, wherein during the calibration period, the control unit is adapted to measure, later than about 50 ms subsequent to application of one of the pacing pulses, an electrical response of the heart to the pacing pulse.

71. Apparatus for improving the performance of the heart of a human subject using a first ventricular electrode and a second ventricular electrode, coupled respectively to a first ventricular site and a second ventricular site of the heart, the apparatus comprising a control unit, which is adapted to drive the first ventricular electrode to

apply one or more paired pulses at the first ventricular site and to drive the second ventricular electrode to apply one or more paired pulses at the second ventricular site.

72. Apparatus for improving the performance of the heart of a human subject using a first electrode, coupled to a first site of a chamber of the heart, and a second electrode, coupled to a second site of the chamber, the apparatus comprising a control unit, which is adapted to drive the first electrode to apply one or more paired pulses at the first site and to drive the second electrode to apply one or more paired pulses at the second site.

FIG. 1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72
28
RA
36
LA
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34
RV
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74
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LV
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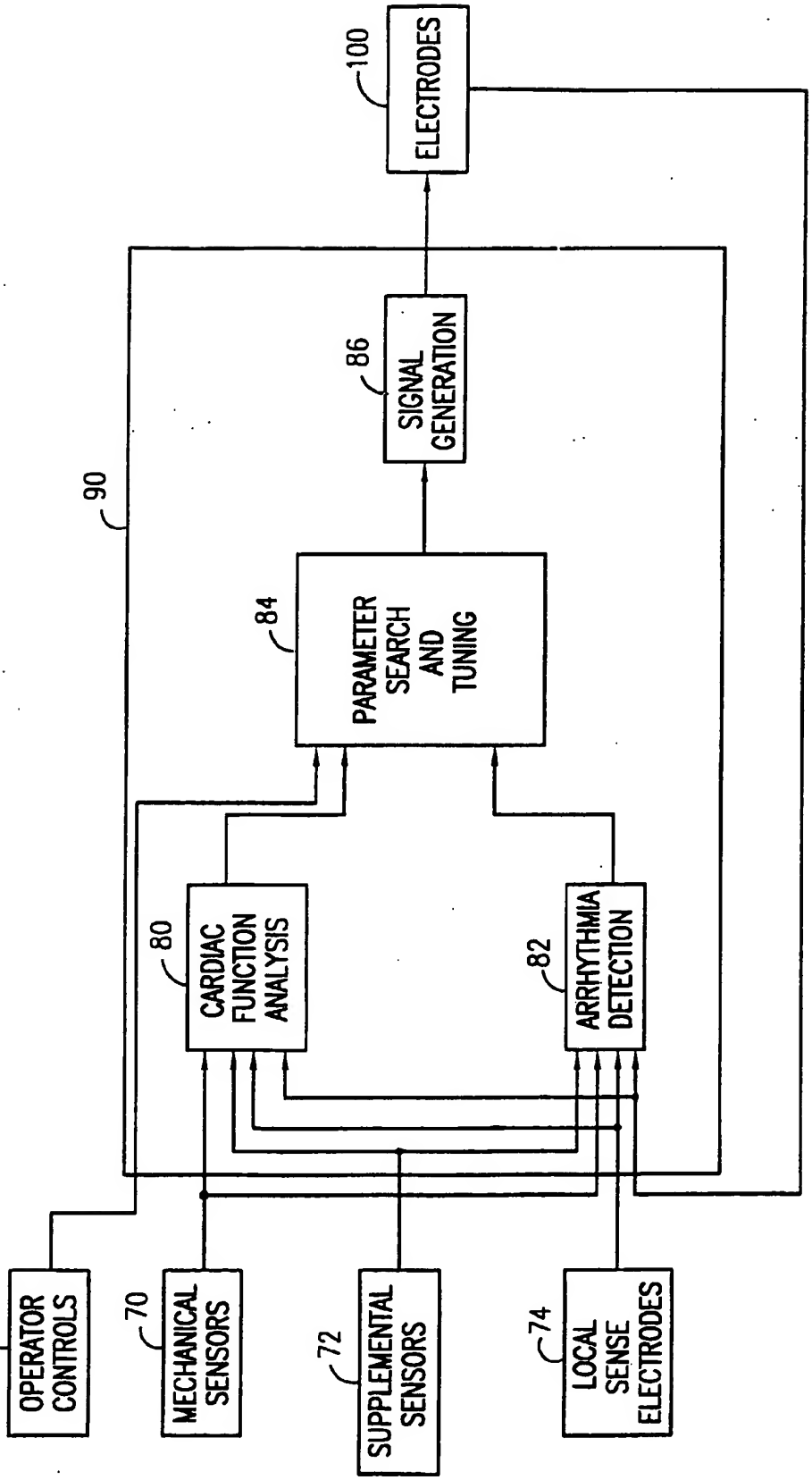
CONTROL UNIT
18

FIG. 2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SIGNAL GENERATION
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71
OPERATOR CONTROLS
70
MECHANICAL SENSORS
72
SUPPLEMENTAL SENSORS
74
LOCAL SENSE ELECTRODES

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(74) Agent: SANFORD T. COLB & CO.; P.O. Box 2273, 76122 Rehovot (IL).

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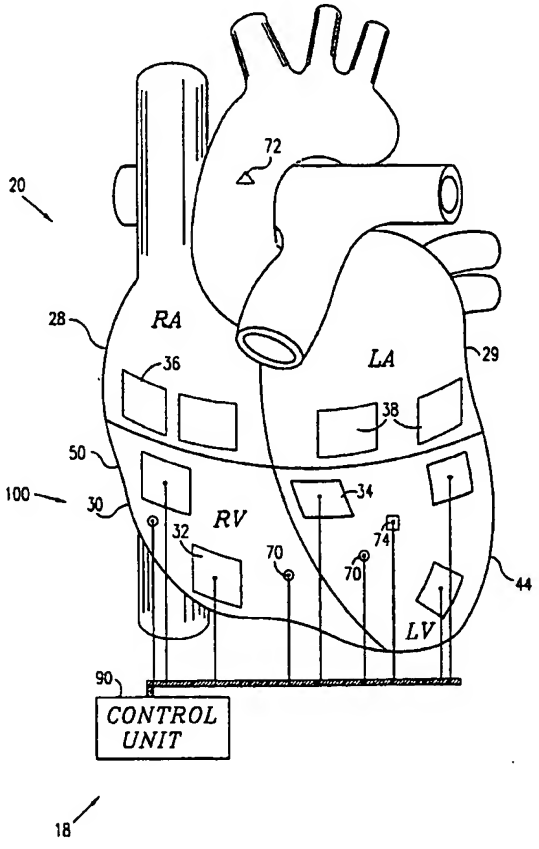
(54) Title: CARDIAC CONTROL USING PAIRED PACING



(57) Abstract: Apparatus (18) for improving the performance of the heart (20) of a human subject. A first ventricular electrode (32) is coupled to a first ventricular site of the heart, and a second ventricular electrode (34) is coupled to a second ventricular site of the heart. A control unit (90) drives the first ventricular electrode to apply one or more paired pulses at the first ventricular site and drives the second ventricular electrode to apply one or more paired pulses at the second ventricular site.

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A. CLASSIFICATION OF SUBJECT MATTER

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US CL :607/148

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 607/9,14-15, 27-28, 119, 123, 129-131,148

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,213,098 A (BENNET et al) 25 May 1993, see entire document.	1-72
Y	US 5,792,208 A (Gray) 11 August 1998, see entire document.	1-72

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Mark Bockelman Telephone No. (703) 308-2112

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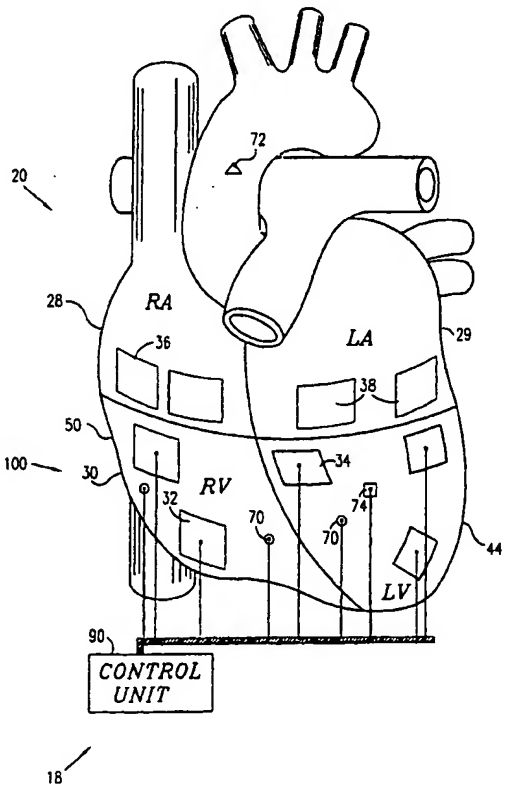

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see PCT Gazette No. 21/2002 of 23 May 2002, Section II

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

REVISED VERSION

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL01/00098

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61N 1/00
US CL :607/148

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 607/9, 14-15, 27-28, 119, 123, 129-131, 148

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,213,098 A (BENNET et al) 25 May 1993, see entire document.	1-72
Y	US 5,792,208 A (GRAY) 11 August 1998, see entire document.	1-72

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
02 JULY 2001

Date of mailing of the international search report
05 MAR 2002

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